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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/405,032	09/24/1999	WILLIAM J. BOYLE	A-378-CIP2C4	9035

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/405,032	BOYLE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61,63-67,69 and 71-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61,63-67,69 and 71-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/19/05 has been entered.

The amendment and response filed 5/19/05 has been entered. Claims 62 and 70 have been canceled. Claims 61, 63-66, 69, 73, 74 have been amended. Claims 61, 63-67, 69, 71-76 are pending and under current examination.

Specification

The specification stand objected because the *status* of the previous U.S. applications to which this application claims priority has not been updated for each and every applications in the continuation chain recited in the first paragraph of the specification. Applicants failed to respond to this objection in the response filed 5/19/05. Appropriate correction is required.

Claim Objections

Claims 61 and 69 are objected to because of the following informalities: step (c) of the method does not belong to the Markush group, as does (a) and (B); and it is not a positive method step but rather the resolve of the method. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 61, 63-67, 69, 71-76 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record and following.

In the remarks, applicants first argue the present specification provides the essential teachings for carrying out the invention, i.e. the nucleic acid encoding an OPG polypeptide, the required materials and procedures were either in the specification or publicly available, and the fact that the actual gene therapy experiments were done after the filing date of the application is irrelevant.

In response, when determining whether the disclosure satisfies the enablement requirements, the Office has considered the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples. In the instant case, a critical

inquiry is whether the gene therapy experiment carried out after the filing date was entirely relied on the teaching of the specification as filed and well known information at the time; or it required knowledge further developed after the filing date, and the answer appears to be the later.

Although the original claims 43-45 contemplate a method for regulating the OPG level or treating bone loss in a mammal comprising administering to the mammal a nucleic acid encoding OPG, the specification only teaches using vectors and ex vivo host cells to produce the OPG protein; while example 3 subtitled as "systemic delivery of OPG to transgenic mouse", the nucleic acid was delivered to single-cell embryos by nuclear transfer, which embryos have not developed into a mammal and do not possess the characteristics of a mammal, accordingly, the claimed invention appears to rely on the state of the art for enablement.

The Office has presented detailed scientific reasons supported by publications from prior and post-filing art for the finding of a lack of enablement in the specification as filed for the claimed invention. A review of prior art of record and the levels of the skilled pointed to an under developed state of the art. (see e.g. *Robbins et al, Orkin et al, Bolon et al, Crystal et al, Miller et al, Deonarain et al, Baylink et al, and Anderson* in the Office action mailed 6/10/03). Moreover, a post-filing publication by applicant's group (*Bolon et al*, 2001, Exhibit C) teaches that in a mouse ovariectomy (OVX) model of estrogen deficiency, only mice that received the adenoviral vector encoding a fusion protein combining the hOPG ligand-binding domain with a human Ig constant domain (Ad-hOPG-Fc), but not the adenoviral vector encoding full-length OPG, developed

serum OPG concentrations exceeding the threshold needed for efficacy, and the OPG persisted for a period sufficient to affect a therapeutic enhancement on bone mineral density in the OVX model. As such, following claims 43-45 as filed, the effect of reducing bone loss would not be obtained because the specification as filed fails to teach the need to use a fusion protein to assert a therapeutic effect, and it fails to disclose the OVX model that could be relied on for evaluating the nucleic acids, and thus the *Bolon* publication provided evidence that the claimed invention would not have been enabled if solely relied on the disclosure of the specification as filed.

Applicants go on to argue that unlike *Genentech Inc. v. Novo Nordisk* A/S, 42 USPQ2d 1005 (CAFC 1997), the art clearly points to certain vectors and methods of administration that are suitable for gene therapy.

The arguments have been fully considered but they are not persuasive for reasons of record and following.

As discussed *supra*, and evidenced by numerous publications in general and *Bolon et al* in particular, using the general concept known at the time of instant effective filing date (1995), a therapeutic effect in treating bone loss will not achieved in a mammal such as in the mouse OVX model. Thus, more specific guidance such as using a fusion protein combining an osteoprotegerin ligand-binding domain with a human immunoglobulin constant domain (2001) is necessary for achieving therapeutic effect of enhancing bone mineral density. Further, the specification fails to teach the vectors suitable for delivering the OPG nucleic acid in a mammal. The types of the vectors and the route of administration are extremely relevant for enabling the claimed invention

because each type of virus has different tissue tropism and each vector system have different efficiency in transducing different types of cells (e.g. See *Robbins et al,* Pharmacol Ther 1998;80:35-47). Taking the adenoviral vector used in the *Bolon* reference as an example, *Robbins et al* teach that the first generation of replication deficient adenoviral vector often stimulates an immune response to the infected cells and results in a loss of therapeutic gene expression in 1-2 weeks, whereas the second generation and completely gutted adenoviral vectors are not available until after the instant priority date (see § 2.2, page 37). Even at a post-filing date, *Bolon et al* teach that the adenoviral vector used is too toxic to hepatocytes, further development of a more desirable vehicle having fewer adverse effects while mediating effective, sustained gene expressing over an extended period of time is necessary before such method could be used in human clinical trial, (last paragraph). Accordingly, the specification as filed is insufficient to support the claimed invention.

In the declaration of Dr. Jackie Sheng, it was indicated that reagents: OPG DNA, human IgGIγ1 DNA, plasmidPACCMVPLPA, plasmid RR5, and 293 human embryonic kidney cell line were available to one skilled in the art before the priority date of the present application. However, having such reagents available does not warrant the success of the claimed invention given the state of the gene therapy art at the time. For example, *Robbins et al* teach that non-viral vectors such as naked DNA (the plasmid mentioned in the declaration) are inefficient in gene transfer to cell nucleus (Section 2, page 36). *Orkin et al* teach naked DNA is extremely inefficient in entry, and no mechanism for persistence or stability. (*Orkin et al,* Dec. 1995, pages 21-23, 30-32).

Thus, the plasmid as indicated in Dr. Sheng's declaration would not be suitable for intravenous delivery needed to reach the target cells, because they are inefficient in cell entry, no capability of targeting the intended cells, and no mechanism or stability for therapeutic efficacy. Moreover, the *Bolon* publication has shown administering to a mammal a nucleic acid encoding the full-length OPG fails to increase the serum OPG to a therapeutic level, and it fails to reduce osteoclast activity or treat bone loss in any mammal. Since the specification fails to teach how to place the critical elements together, since many critical knowledge or reagents were not available at the time of the filing, it would have required undue experimentation for those intending to practice the claimed invention.

The submitted supporting evidence in the post-filing publication also fails to teach whether any of the OPG fragments alone, as recited in the instant claims, would assert any therapeutic effect in treating bone loss. Since Bolon et al publication has provided evidence that the full-length hOPG DNA was not enabled to assert a therapeutic effect, it is more likely than not that the fragments of the hOPG DNA would not asset a therapeutic effect. In view of such, the invention does not appear to be enabled in the absence of clarification of the contradictory evidence found in the references.

In summary, the prior- and post-filing references have shown to achieve a therapeutic effect in treating bone loss, one has to rely on newly developed information such as using the hOPG-Fc fusion protein in place of hOPG along, further optimized vectors, and the OVX animal model, to be able to carry out the claimed invention. Since the original disclosure is silent regarding how to practice the instantly claimed subject

matter, about the fusion protein, an optimized vector, and the animal model to evaluate the pharmacokinetics of the nucleic acids, a later filed declaration and publication could not supplement the essential element that is missing from the specification as filed. As stated in In re Glass, 181 USPQ 31, (CCPA 1974), if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date.

Accordingly, for reasons of record and those set forth foregoing, the specification fails to meet the statutory enablement requirement set forth under 35 U.S.C. § 112.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 61, 63-67, 69, and 71-76 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 11, and

12 of U.S. Patent No. 6,284,740 because the claims of the cited patent encompasses instant claims.

The method claims in the present application and the cited patent are each drawn to a method comprising administering to a mammal a nucleic acid encoding and expressing OPG for treating bone loss (or increase bone density). Claims 2 and 12 explicitly recite the human osteoprotegerin, which is fully disclosed in figures 9C-D of the cited patent.

The processes of the present application and the cited patent differ one from the other in that instant claims recite specific fragments of SEQ ID No: 124 (hOPG) which were not claimed in the cited patent. However, these fragments are fully disclosed in the cited patent (e.g. figs. 9C-D, 11, and paragraph bridging columns 7 & 8).

Accordingly, the claimed processes in the copending and the present application are obvious variants, and the inventions as claimed are co-extensive.

In the response filed 5/19/05, applicants argued that the Examiner's position on double patenting is inconsistent with the enablement rejection, because the present application is a CIP of the cited patent, and cannot be enabled in one but not the other.

As an initial matter, it is noted the cited patent is not a part of the continuation chain recited in the first paragraph of the instant application, and the instant application does not claim priority to the cited patent, and thus the cited patent is unrelated to the instant application.

As to the enablement of the claims in the cited patent, Applicants are reminded each application is examined on its own merits and cannot be compared to other

application. The court (*In re Giolito and Hofmann*, 188 USPQ 645 (CCPA 1976)) states "IT IS IMMATERIAL WHETHER SIMILAR CLAIMS HAVE BEEN ALLOWED TO OTHERS. SEE IN RE MARGAROLI, 50 CCPA 1400, 318 F.2D 348, 138 USPQ 158 (163); IN RE WRIGHT, 45 CCPA 1005, 256 F.2D 583, 118 USPQ 287 (158); IN RE LAUNDER, 41 CCPA 887, 212 F.2D 603, 101 USPQ 391 (1954)." Rather, it is applicant's duty to provide an enabling disclosure for what is now claimed in this application.

Applicants also indicated they would consider filing a terminal disclaimer to obviate this rejection if all other issues be resolved. Until then, the rejection stands.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The fax numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
August 8, 2005